

Dear Editor,

We would like to thank you and the reviewers for reading our manuscript and reviewing it. We are very happy to resubmit the revised manuscript of “Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C”. Following your instructions and suggestions, this document was prepared and we resubmit it. We provide point by point the answers to the reviewers’ comments.

## **REVIEWER 1**

### ***Comment 1***

Authors should mention that establishment of HBV infection and its replication space is limited by the antiviral effects of type I interferon in the chronically HCV-infected liver (Wieland SF, et al. J Virol 2014;88:5184-8).

### ***Answer 1***

We thank the reviewer for this comment. We have added this observation in the Discussion section (page 9, line 25).

### ***Comment 2***

Without DAAs, reappearance of serum hepatitis B viral DNA in patients with hepatitis B surface antigen seroclearance are occasionally observed (Nakamura M, et al. Hepatology. 2015 Oct;62(4):1329. doi: 10.1002/hep.27693.).

### ***Answer 2***

We have added this comment in the Introduction section (page 5, line 16).

### ***Comment 3***

Authors should distinguish between HBV reactivation and HBV DNA reappearance.

***Answer 3***

We have re-written the term of HBV reactivation in the Introduction section in order to be better distinguished the difference between HBV reactivation and HBV DNA reappearance (page 5, line 10).

***Comment 4***

In Table 1, authors should describe the ALT levels.

***Answer 4***

The ALT levels before DAA treatment and at initiation of HBV reactivation have been added to the table 1.

***Comment 5***

Authors should rewrite the text in page 5, "...Recent studies have reported that treatment with direct-acting antivirals (DAA) for hepatitis C virus (HCV) treatment may cause HBV reactivation in patients with coinfection [15-21]...."

***Answer 5***

The above sentence has been replaced by: Hepatitis with alanine transaminase (ALT) elevation due to reactivation of HBV has been reported in HCV/HBV co-infected patients who were treated with direct-acting antiviral (DAA) regimens for chronic hepatitis C virus (HCV) infection

**REVIEWER 2**

***Comment 1***

Please provide the recommended treatment algorithm for those with the coinfection of HBV and HCV in a figure.

***Answer 1***

We have provided a treatment algorithm where we have summarized the available treatment options for co-infected individuals. This figure (figure 1) is accompanied by an informative legend where we have discussed to a certain extent the different

available options and related issues. This information has been added in the Discussion section (page 11, line 28).

### **REVIEWER 3**

#### ***Comment 1***

Discussion section: 2<sup>nd</sup> paragraph, line 6: "In particular, patients with chronic HBV who developed HCV have shown decreased HBV replication "--- It will be better to re-write this sentence for better understandable

#### ***Answer 1***

The above sentence has been replaced by: "In particular, most HBV-infected individuals who develop HCV have decreased HBV replication due to the suppression effect of HCV on HBV infection.

#### ***Comment 2***

EASL guidelines suggest that if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients ("occult" hepatitis B), concurrent HBV nucleoside /nucleotide analogue therapy is indicated. But AASLD guidelines suggest the patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually not more frequently than every 4 weeks) and initiate HBV therapy when DNA levels meet treatment criteria. --- It would be better to provide the author's expert view-point to comment about this difference between two official guidelines. A little more pros and cons discussion about treat immediately or treat until DNA levels meet treatment criteria may help the readers.

#### ***Answer 2***

We have added a figure in which the different treatment options for the HBV-HCV coinfection are included (figure 1). Moreover we have added in the Discussion section (page 11, line 28) a discussion on factors that could affect our decision making. We have attempted to instill the notion of the reader that every patient should be

addressed case – by – case basis and that is imperative that physicians have options that could adjust their approach on this.

***Comment 3***

The Chinese author Wang's observation study find that when clinical hepatitis occurred in HCV/occult HBV co-infected group, it is not related to HBV reactivation, but rather related to intake of herb or binge of alcohol. It would be helpful to put it in discussion section to provide differential diagnostic thinking alternatives.

***Answer 3***

We thank the reviewer for this comment. We have added a paragraph in the Discussion section describing the cases of hepatitis development due to other factors than HBV reactivation (page 9, line 5).

**REVIEWER 4**

***Comment 1***

It is standard that generic drug names start with a small letter e.g tenofovir not Tenofovir. DAA versus DAAs – one is singular, the other is plural and singular should be used as appropriate throughout the article. Data is plural - it should be 'these data' not 'this data'. Standard procedure when writing journal articles is to explain an abbreviation in brackets the first time it is used – this should be done for all HBV serology abbreviations used in the article e.g HBsAg (hepatitis B surface antigen).

***Answer 1***

We have made the proper changes as suggested. Moreover, our manuscript has checked by a professional English language editing company and we have submitted a language certificate.

**Additional comments**

The manuscript has been revised according to the reviewers' comments. All the revisions are cited in the response letter and are highlighted in the updated version of the manuscript. We have attached the core tip in an audio form (mp3) and the Google Scholar search. For the Google Scholar search we have attached a document with the first page of the results where you can find the link with the additional pages as there are numerous pages of related documents. As far as the foundation is concerned, there are no grants to declare. A language editing certificate has also been attached to verify that the language of the manuscript has reached Grade A. The copy right assignment and the undersigned by the corresponding author conflict of interest statement have been attached with the revised manuscript as well as all the related documents. Lastly, in the edited manuscript we found a comment about the adding of "Comments section" according to the format. However, we did not find this section in the editorial format; hence we did not add it in our manuscript. If you suggest that the "Comments" section is needed in the editorial format, please let us know in order to prepare it.

Yours sincerely

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